II. AMENDMENTS TO THE SPECIFICATION

--- The location of each paragraph to be deleted or replaced, and where the new paragraph or section is to be added, is set forth unambiguously below. A marked-up version of any replacement paragraph is provided. The text of new paragraphs or sections is not underlined. Any amendment (if any) to the abstract is treated as any other amendment to the specification.

- *THE SPECIFICATION OF THE PATENT IS HEREBY AMENDED AS SET FORTH BELOW:*

  - Please delete paragraph **[0009]** and replace with the paragraph below. A marked up version is provided as required:

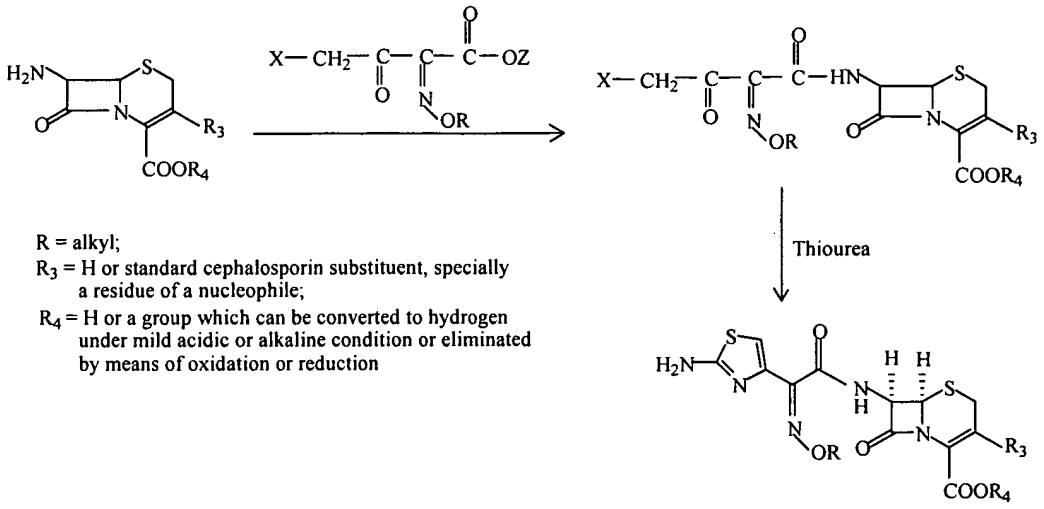
[0009] Synthesis of ceftriaxone (I) as per Method-[[I1]] II is equally widely documented in the literature. Several methods, varying subtly in the choice of the reactive group Z of compounds of formula (C) have been utilised, albeit the choice of the activating group is primarily restricted to acid halides. A few such methods are:

(a) U.S. Patent No. 5,109,131 describes a process for preparation of 7-[2-(2-amino thiazol-4-yl)-oxyimino acetamido cephalosporin compounds, carrying a "residue of a nucleophile" in the 3α-position, which includes *inter alia* ceftriaxone. The method utilizes tert-butyl-3-oxobutyrate as an intermediate, which is reacted as such or a reactive derivative thereof is reacted with compound of formula (A) to form the 7-substituted cephalosporin addendum (D), which on reaction with thiourea gives ceftriaxone. The reactive derivatives utilised for 7-amidification as disclosed in U.S. Patent No. 5,109,131 include acid halides, a mixed acid anhydride, an active amide or an active ester. The chemistry is summarized as shown hereinbelow in Scheme-[[I1]] II.

(b) European Patent No. 0,030,294 (and its equivalent in Canada, CA 1 146 165) claims ceftriaxone and its esters and a process for preparation thereof comprising the following steps as described in Example-1 of said patent i.e.

b.1 reacting (7R)-Amino-3-desacetoxy-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid (corresponding to Compound A of Scheme-I) with N,O-bis-(trimethylsilyl)-acetamide in ethyl acetate at 25° C for 30 minutes to form the corresponding (N,O)-bis-silyl derivative;

b.2 addition of a solution of 4-bromo-2-methoxyimino-3-oxo-butyryl chloride (Corresponding to Compound C of Scheme-I) in dichloromethane to the solution of the (N,O)-bis-silyl derivative in ethyl acetate thus obtained in step b.1 and after work up, crystallization of the residue from etherpetroleum ether to give (6R,7R)-7-[[4-Bromo-2-(Z)-methoxyimino]acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid [corresponding to compound (D) of Scheme-I];



Scheme-II : Process disclosed in US Patent No. 5 109 131

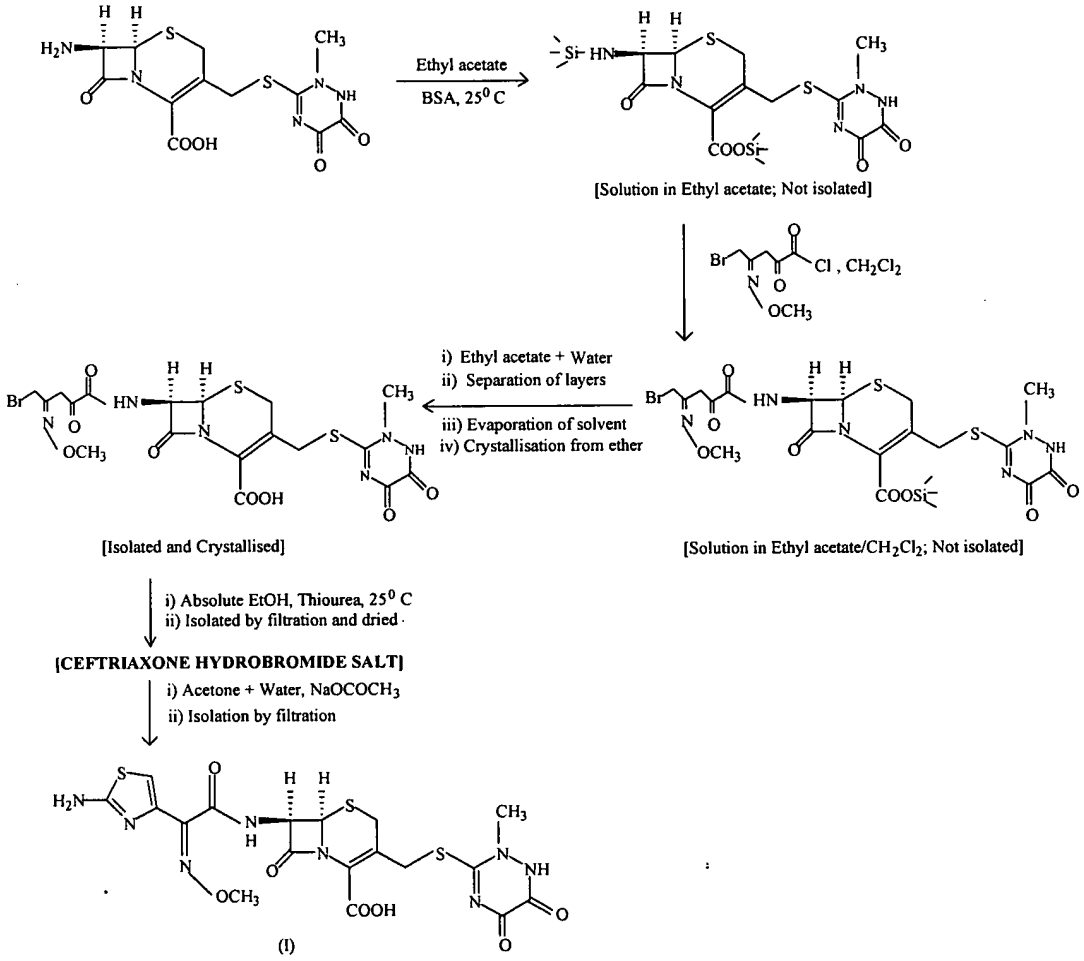
b.3 reaction of the (6R,7R)-7-[[4-Bromo-2-(Z)-methoxyimino]acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid obtained above with thiourea in absolute alcohol to give the hydrobromide salt of ceftriaxone; and

b.4 neutralisation of ceftriaxone hydrobromide salt with sodium methoxide in a mixture of water and acetone to give ceftriaxone (I), which is isolated by filtration.

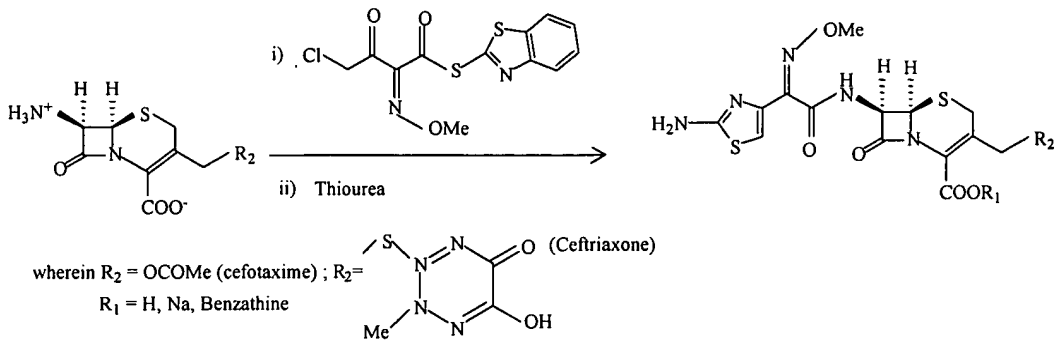
The chemistry disclosed in EP Patent No. 0,030,294 is summarized in Scheme-III.

(c) European Patent No. 0,842,937 claims a process for preparation of ceftriaxone and cefotaxime comprising reaction of 7-amino-3-desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid (compound III of Scheme-I) and 7-ACA respectively with 4-chloro-2-

methoxyimino-3-oxobutyric acid, activated as 2-mercaptobenzothiazolyl ester, followed by cyclization of the intermediate thus obtained with thiourea to give ceftriaxone and cefotaxime respectively. The chemistry disclosed in EP Patent No. 0,842,937 is summarized in Scheme-IV.



Scheme-III : Method of preparation of ceftriaxone as disclosed in EP Patent No. 0 030 294



Scheme-IV : Preparation of ceftriaxone as disclosed in EP Patent No. 0 842 937

(d) The process disclosed in EP Patent No. 0,556,768 essentially is an improvement over the one described in EP Patent No. 0,842,937, wherein the method for preparation of ceftriaxone comprises reaction of 7-amino-3-desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid (compound A of Scheme-I) with 4-chloro-2-methoxyimino-3-oxobutyric acid, activated as 2-mercaptobenzothiazolyl ester, followed by cyclization of the intermediate ~~thus obtained with thiourea~~ to give ceftriaxone. The improvement this patent claims is that the abovementioned reaction and subsequent conversion of ceftriaxone to its disodium hemiheptahydrate salt can be carried out in one pot using a mixture of acetone and water as solvent.

(e) U.S. Patent No. 6,384,215 provides yet another variation, wherein the compound V of Scheme-I is activated as a 2-mercapto-5-substituted-1, 3,4-oxadiazole derivative prior to 7-amidification, followed by cyclization of the intermediate compound thus obtained with thiourea to give ceftriaxone.

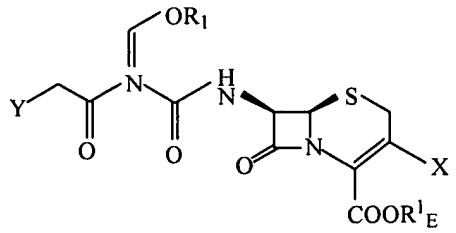
(f) The recently issued U.S. Patent No. 6,552,186 B2 claims a method for preparation of ceftriaxone comprising reaction of (N,O)-bis silylated 7-amino-3-

desacetoxy-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)-thio]-3-cephem-4-carboxylic acid (compound A of Scheme-I) with 4-halo-2-methoxyimino-3-oxobutyric acid, suitably activated as a reactive derivative (compound C of Scheme-I) to give the corresponding intermediate 7-acylated compound (D of Scheme-I, wherein the group R_1 attached to the carboxylic acid function at the 4-position is a trialkyl silyl group), followed by either,

(i) reaction of the 7-acylated compound (D of Scheme-I, wherein the group R_1 attached to the carboxylic acid function at the 4-position is a trialkyl silyl group), with silylated thiourea to form the aminothiazole ring, which after necessary desilylation gives ceftriaxone, (as claimed in claim 3a of said patent); or

(ii) desilylation of the 7-acylated compound (D of Scheme-I, wherein the group R_1 attached to the carboxylic acid function at the 4-position is a trialkyl silyl group), followed by reaction of the desilylated compound thus obtained with thiourea to give ceftriaxone (as claimed in claim 3a of said patent).

In addition, the U.S. Patent No. 6,552,186 B2, claims the 7-acylated compound (D of Scheme-I, wherein the group R_1 attached to the carboxylic acid function at the 4-position is a trialkyl silyl group) as represented in Chart-I hereinbelow as a novel compound.



wherein
R_1 is unsubstituted alkyl or alkyl

R^1_E is trialkyl silyl or denotes with the COO to which R^1_E is attached is an ester
Y = halogen
X is a group of formula
R" is trialkyl silyl

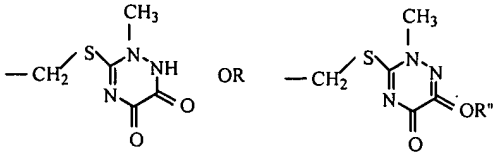


Chart-I: Compound claimed in claim 1 of US Patent No. 6 552 186 B2

The U.S. Patent No. 6,552,186 B2 further claims that the reaction of the desilylated compound with thiourea is effected in the presence of a solvent system containing an organic solvent and water to give ceftriaxone.

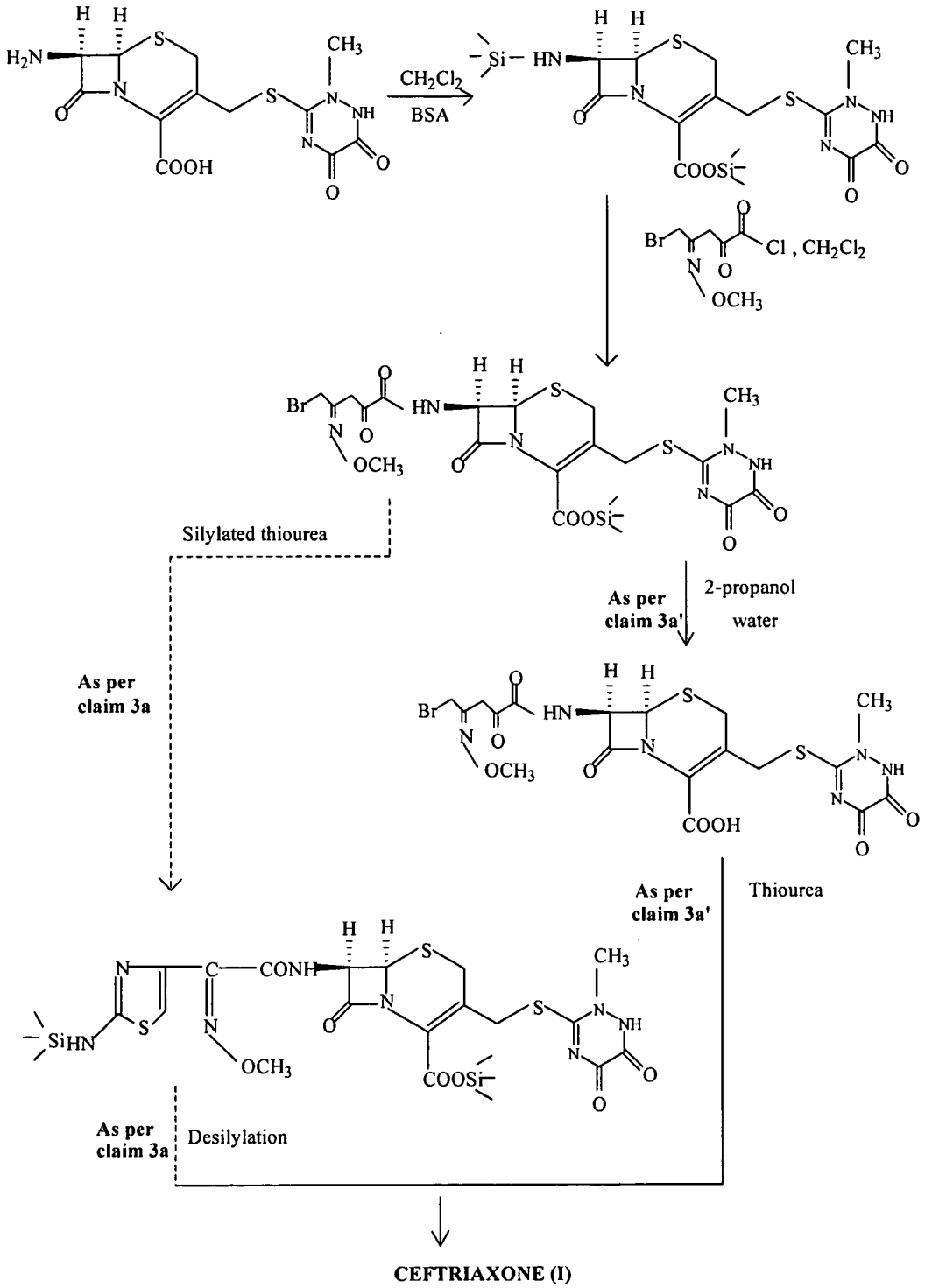
The chemistry claimed in claims 3a and $3a^1$ of the U.S. Patent No. 6,552,186B2 for synthesis of ceftriaxone is summarized in Scheme-V. However, the chemistry embodied in claim $3a^1$ of the U.S. Patent No. 6,552,186 B2 not only lacks novelty but is anticipated from the prior art methods discussed hereinbefore as well as those summarized hereinbelow, as would be apparent to a person skilled in the art from the discussion contained hereinbelow:

f.1 The invention apparently residing in U.S. Patent No. 6,552,186 B2 is use of a silylated compound i.e. (6R,7R)-7-[[4-Bromo-2-(Z)-methoxyimino] acetamido]-3-[(2,5-dihydro-6-

hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid, wherein the carboxylic acid function is silylated for subsequent reaction with,

(a) silylated thiourea to give ceftriaxone after desilylation (as claimed in Claim 3 a of said patent); or

(b) desilylation of the silyl compound and reaction of the desilylated compound thus obtained with thiourea to give ceftriaxone (as claimed in Claim $3a^1$ of said patent).



Scheme-V : Preparation of ceftriaxone as per the method disclosed in US Patent No. 6 552 186 B2

f.2 However, the said chemistry is identical and superimposable to that disclosed in Example-1 of EP Patent No. 0,030,294, summarized in Scheme-III, which, needless to mention has an early priority of nearly twenty years than the priority date of U.S. Patent No. 6,552,186 B2.

The only difference in both the processes is in the choice of solvents, reaction temperatures and mode of isolation of the product. However, both the methods function the same way giving substantially the same result, thereby indicating that the change in parameters and solvents are inconsequential and have no bearing in the course of the reaction.

f.3 Moreover, the compound claimed in claim 1 of U.S. Patent No. 6,552,186 B2 (as summarized in Chart-I) lacks novelty since the same compound is obtained and reported, albeit not specified in the process embodied in Example-1 of EP Patent No. 0,030,294.

f.4 Further, that portion of claim $3a^1$ of U.S. Patent No. 6,552,186 B2 claiming that the reaction of the desilylated compound with thiourea is effected in the presence of a solvent system containing an organic solvent and water to give ceftriaxone also is anticipated from the teachings of U.S. Patent No. 5,109,131, wherein a mixture of organic solvent and water i.e. mixture of tetrahydrofuran and water has been specified and

used for cyclization of a structurally similar compound with thiourea for formation of the aminothiazolyl addendum at the 7-amino position, as evident from WORKING EXAMPLE 3 (4), column 13 of said patent.

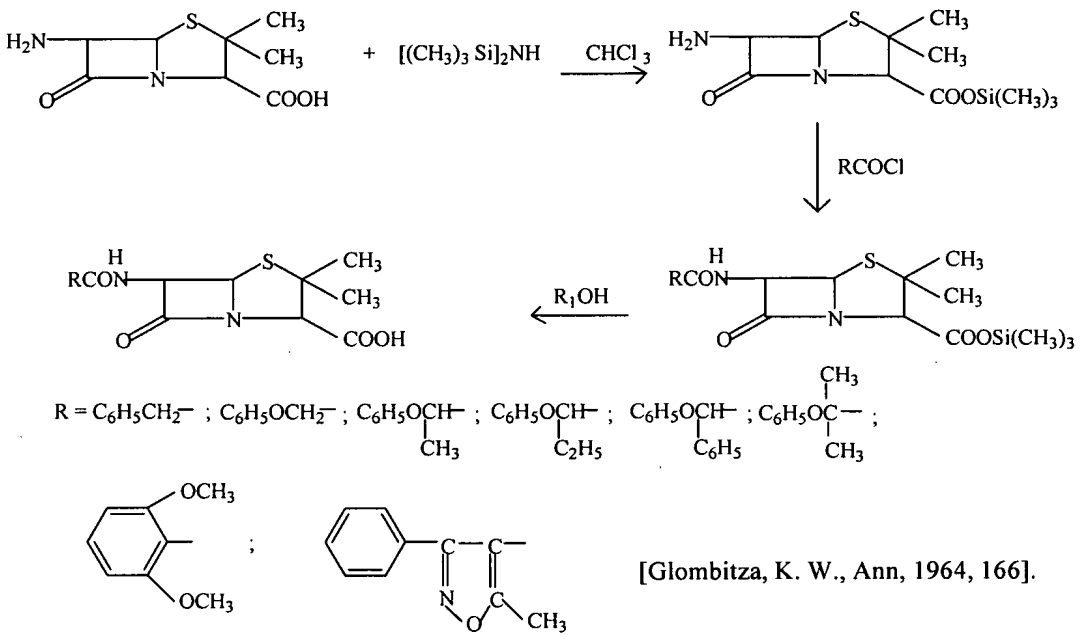
f.5 With regard to protection of the carboxylic acid function at 4-position of a cephalosporonic acid derivative as a trialkylsilyl group prior to amidification at 7-position as claimed in Claim 3a[1] of U.S. Patent No. 6,552,186 B2 it can be termed at the most "trivial" and not substantially contributing to the development of cephalosporin chemistry in any way. Similarly, deprotection of the said "trialkylsilyl" protective group is also "trivial" and has no substantial bearing in the course of the reaction.

There is a wealth of literature, wherein the carboxylic acid function at 4-position and/or the amino function at 7-position of a cephalosporin derivative have been protected through silylated derivatives prior to amidification. From these, it would be abundantly evident that claims for protection and deprotection through silylation residing in U.S. Patent No. 6,552,186 B2 is not novel and is anticipated and obvious to a person skilled in the art.

Protection of reactive functional groups, specially the carboxylic acid function at 4-position and the amino function at

7-position through silylation is widely practiced in cephalosporin chemistry since many years. As early as 1964 acylation of 6-aminopenicillinate esters (6-APA) to give commercially valuable antibiotics such as ampicillin and amoxycillin have been achieved through protection of the carboxylic acid function at 3-position as trialkyl silyl esters [Glombitza, K. W., *Ann*, 1964, 166].

This publication teaches acylation of 6-aminopenicillinate (6-APA) esters having an easily removable carboxyl protecting group and, therefore, soluble in organic solvents. The author discovered that 6-APA trialkyl silyl esters could be readily obtained by reacting 6-APA with hexamethyldisilazane in chloroform and the ester thus obtained could be successfully acylated with acid chlorides or by the mixed anhydride method. The advantage cited is that the silyl group could be removed merely by treatment with water during the workup procedure. Several penicillins were synthesized in high yields (65-98%) by this method, which is summarized in Scheme-VI.



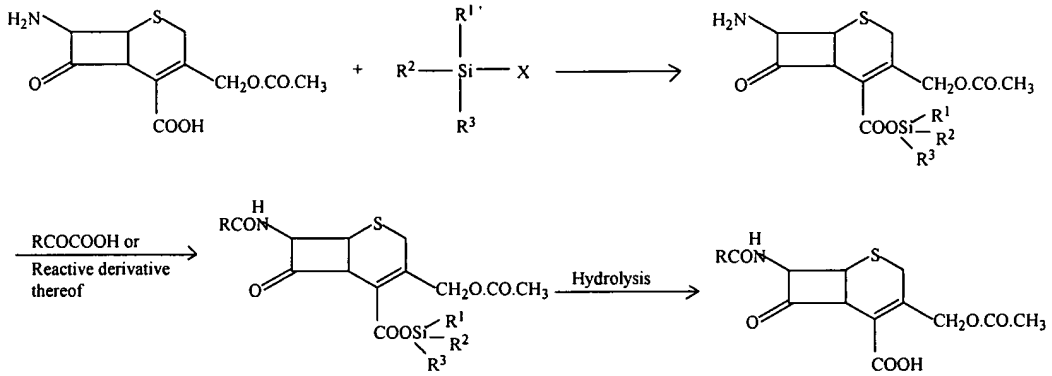
[Glombitza, K. W., Ann, 1964, 166].

Scheme-VI : The acylation of penicillins as disclosed by Glombitza, K. W. in Ann, 1964, 166

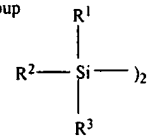
Similarly, an improved method for preparation of 7-acylamidocephalosporanic acids by acylation of the 7-ACA esters was reported as early as 1963, wherein the inventors have claimed that best results were achieved by silyl esters of 7-ACA since the ester group was easily removed by mild acidic work-up (Jackson et. al., GB Patent No. 1,073,530).

This patent teaches an improved procedure for the preparation of 7-acylamidocephalosporanic acids by acylating the 7-ACA esters which are soluble in organic solvents. The patent claims that best results were achieved by using the silyl esters of 7-ACA since the ester group was easily removed by mildly acidic conditions during the workup procedure.

The chemistry is summarized in Scheme-VII.



R^1, R^2, R^3 = Alkyl group of 1-6 carbon atoms ; X = Halogen or a group NR^4R^5 , wherein R^4 and R^5 are hydrogen or an alkyl group of 1-6 carbon atoms or a group



Scheme-VII : the acylation method of cephalosporins disclosed in GB Patent No. 1 073 530

(g) In addition, replication of the prior art methods, specially the process embodied in Example-2 of U.S. Patent No. 6,552,186 B2 for preparation of ceftriaxone sodium is found to be associated with the following shortcomings in that:

g.1 the reaction (N,O)-bis trialkylsilyl 7-amino-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl]-3-cephem-4-carboxylic acid with 4-halo-2- methoxyimino-3-oxo-butyric acid halide to give (6R,7R)-7-[[4-halo-2-(Z)-methoxyimino]acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid trialkylsilyl ester, does not proceed to completion and about 10% of starting compound i.e. (N,O)-bis trialkylsilyl 7-amino-3-[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl]-3-cephem-4-carboxylic acid remains unreacted,

g.2 precipitation of ceftriaxone occuring during reaction of (6R,7R)-7-[[4-halo-2-(Z)-methoxyimino]acetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid (after subsequent hydrolysis of the trialkylsilyl carboxylic ester) with thiourea, which not only because of the incompletion of reaction in the precursor step but also because of formation of higher level of impurities in the reaction result in production of ceftriaxone in lower yield, and of unsatisfactory quality and

g.3 conversion of ceftriaxone thus produced to ceftriaxone sodium is found to give a Colored product i.e. very high Color absorbance of 1.0 to 1.8 AU at 450 nm, having a purity of about 73-80%, and containing higher level of impurities,

all contributing to and resulting in production of ceftriaxone and ceftriaxone sodium of quality and nature not conforming to pharmacopoeial specifications and therefore, rendering the product not only unsuitable for formulation into a dosage form but also for administration to human beings.